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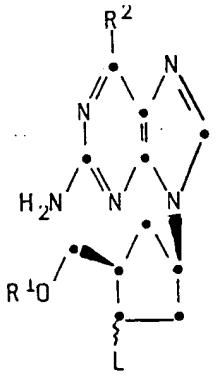
(54) Title: SYNTHESIS OF CYCLOPENTENE DERIVATIVES



(II)

(57) Abstract

A process is described for the preparation of the 1R-cis isomer of carbovir, [1'R,4'S]-2-amino-9-[4-(hydroxymethyl)-2-cyclopenten-1-yl]-1,9-dihydro-6H-purin-one and its physiologically acceptable salts from a compound of formula (II) (where L represents a leaving group, R^1 represents a hydrogen atom or a hydroxyl protecting group and R^2 represents OH, NH_2 or a protected hydroxyl group). The 1R-cis isomer of carbovir is an antiviral agent with potent activity against human immunodeficiency virus (HIV).

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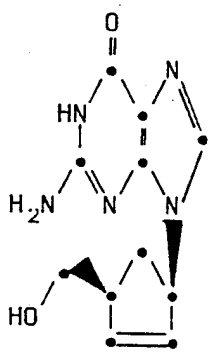
SYNTHESIS OF CYCLOPENTENE DERIVATIVES

This invention relates to a new process for the preparation of certain optically active purine substituted cyclopentene derivatives and novel intermediates used in this process. In particular, the invention describes the synthesis of the 1R-cis isomer of carbovir, [1'R,4'S]-2-amino-9-[4-(hydroxymethyl)-2-cyclopenten-1-yl]-1,9-dihydro-6H-purin-6-one, an antiviral agent.

GB-A-2217320 discloses a group of antiviral purine substituted cyclopentene derivatives including the 1R-cis isomer of carbovir, [1'R,4'S]-2-amino-9-[4-(hydroxymethyl)-2-cyclopenten-1-yl]-1,9-dihydro-6H-purin-6-one, a compound of the formula (I)

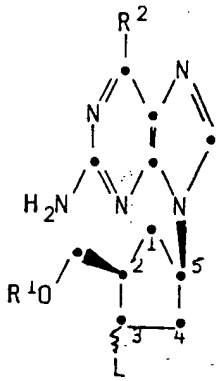


(I)

together with processes for their preparation.

The compound of formula (I) (also referred to hereinafter as (-)-carbovir) has been found to have potent activity against human immunodeficiency virus (HIV) associated with acquired immune deficiency syndrome (AIDS) [see Vince, R., et al., Biochem. Biophys. Res. Commun., 156(2), 1046 (1988)]. There is however a need for improved synthetic routes to (-)-carbovir from relatively inexpensive starting materials.

We have now found a novel efficient process for preparing the compound of formula (I). Thus, according to one aspect of the present invention, we provide a process for the preparation of the compound of formula (I) and physiologically acceptable salts thereof, which comprises reacting a compound of formula (II)

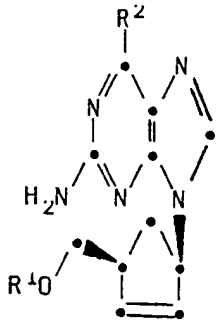


(II)

(wherein L is a leaving group, R^1 is a hydrogen atom or a hydroxyl protecting group and R^2 is OH, NH_2 or a protected hydroxyl group) to convert the leaving group L therein to a 3 ,4 -ene group, followed by conversion of R^2 and/or OR^1 to hydroxyl groups as appropriate, with salt formation as an optional subsequent step.

Examples of leaving group L include OH, OSO_2R^3 (where R^3 represents alkyl, for example C_{1-6}alkyl such as methyl; aryl, for example phenyl or tolyl; or trifluoromethyl), SeR^4 (where R^4 represents aryl, for example phenyl) or halogen (e.g. bromine or iodine).

The elimination of HL provides a compound of formula (III)



(III)

wherein R^1 and R^2 are as defined above.

Suitable conditions for the conversion of compounds of formula (II) to compounds of formula (III) will of course depend upon the nature of the leaving group L. Thus, for example, when L represents OH the elimination reaction may be effected by methods such as those referred to in "Compendium of Organic Synthetic Methods", Eds. I. T. Harrison and S. Harrison, Wiley-Interscience, 1971, pp. 484-488. When

L represents a halogen atom the elimination reaction may be effected by methods such as those referred to in "Compendium of Organic Synthetic Methods", Eds. I. T. Harrison and S. Harrison, Wiley-Interscience, 1971, pp. 507-510.

We have found that compounds of formula (II) in which L represents OSO_2R^3 or SeR^4 (where R^3 and R^4 are as defined above) are particularly convenient precursors to the compounds of formula (III). Such compounds in which L represents OSO_2R^3 may be converted to compounds of formula (III) by treating the appropriate compound of formula (II) with a base, for example an alkali metal alkoxide (e.g. sodium methoxide or $NaOCH_2CH_2OCH_3$) in a suitable solvent such as an amide (e.g. dimethylformamide), or a quaternary ammonium salt such as a tetraalkylammonium halide (for example a tetrabutylammonium halide such as tetrabutylammonium fluoride) in a solvent such as an ether (e.g. tetrahydrofuran). The elimination reaction involving a compound of formula (II) in which L represents OSO_2R^3 may be carried out at any suitable temperature and conveniently at 0^0C to ambient temperature.

Compounds of formula (II) in which L represents SeR^8 may be converted to compounds of formula (III) by treating the compound of formula (II) with a peroxide oxidising agent such as hydrogen peroxide in a solvent such as an ether (e.g. tetrahydrofuran) conveniently at a temperature between 0^0C and ambient temperature.

Compounds of formula (III) in which OR^1 and/or R^2 represent protected hydroxyl groups may conveniently be converted to (-) carbovir by deprotection means. When two protecting groups are present deprotection at the purine ring 6-position is conveniently effected prior to removal of the other protecting group.

Compounds of formula (III) in which R^2 represents NH_2 or OH may conveniently be converted to (-) carbovir by removal of the R^1 protecting group, followed when R^2 represents NH_2 by conversion of the NH_2 group to OH.

Removal of the hydroxyl protecting groups may be effected by conventional means. Thus, for example, alkyl, silyl, acyl, alkoxyalkyl and heterocyclic groups may be removed by solvolysis, e.g. by hydrolysis under acidic or basic conditions. Aralkyl groups such as

triphenylmethyl may similarly be removed by solvolysis, e.g. by hydrolysis under acidic conditions. Aralkyl groups such as benzyl may be replaced by acyl (e.g. acetyl) groups using a carboxylic acid anydride such as acetic anhydride which, in turn, may be removed by solvolysis. Conveniently, acyl groups such as acetyl may be removed by hydrolysis under basic conditions, for example using an alkali metal alkoxide (e.g. sodium ethoxide) or using an ammonia/methanol mixture. Conveniently, alkoxyalkyl groups such as methoxyethyl may be removed under mild acid conditions, for example using a Lewis acid such as aluminium triiodide in a solvent (e.g. acetonitrile) at elevated temperature (e.g. at reflux).

Conversion of (1S,4R)-4-[2,6-diamino-9H-purin-9-yl]-2-cyclopentenemethanol to (-) carbovir may be effected by hydrolysis, and preferably by treating the 2,6-diamino compound with a suitable enzymatic hydrolysing system such as adenosine deaminase adjusted to a pH in the range pH 6 to 8 (e.g. at about pH 7.5) and conveniently buffered to the desired pH using for example disodium orthophosphate. The reaction may be carried out at any suitable temperature and conveniently at 20° to $50^{\circ}C$. The reaction may also be carried out in the presence of a suitable solvent such as water or an alcohol-water mixture, e.g. glycerol-water.

Compounds of formula (II) in which L represents a leaving group other than OH may be prepared from compounds of formula (II) in which L represents OH. The conversion of the 3-OH group to a different leaving group may be effected by a conventional displacement reaction. Thus, for example, compounds of formula (II) in which L represents a group OSO_2R^3 (where R^3 is as previously defined) may be prepared from compounds of formula (II) in which L represents OH by reaction with a sulphonyl halide of the formula R^3SO_2Hal (where R^3 is as previously defined and Hal is a halogen atom, e.g. chlorine). This particular displacement reaction may conveniently be effected in a solvent such as a halogenated hydrocarbon (e.g. dichloromethane) at a temperature in the range -10° to $+50^{\circ}C$ (e.g. at about $0^{\circ}C$). The reaction preferably takes place in the presence of a base such as an amine

(e.g. triethylamine or 4-dimethylaminopyridine) or a mixture of amine bases.

When L represents SeR^4 (where R^4 is as previously defined) such compounds of formula (II) may be prepared via compounds of formula (II) in which L represents OSO_2R^3 (where R^3 is as previously defined, e.g. methyl). The conversion of the group OSO_2R^3 to SeR^4 may conveniently be effected by reaction of the compound of formula (II) in which L represents OSO_2R^3 with $NaSeR^4$ (where R^4 is as previously defined) in a suitable solvent such as an ether (e.g. tetrahydrofuran).

Compounds of formula (II) in which L represents OH may be prepared from a corresponding protected hydroxy compound by removal of the protecting group according to the general methods described above.

The protecting group referred to hereinabove may represent any conventional hydroxyl protecting groups, for example, as described in 'Protective Groups in Organic Chemistry', Ed. J. F. W. McOmie (Plenum Press, 1973) or 'Protective Groups in Organic Synthesis' by Theodora W. Greene (John Wiley and Sons, 1981). Examples of suitable protecting groups include groups selected from alkyl (e.g. methyl or t-butyl), alkoxyalkyl (e.g. methoxymethyl or methoxyethyl), aralkyl (e.g. benzyl, diphenylmethyl or triphenylmethyl), substituted aralkyl wherein the aryl portion of the aralkyl group may be substituted by, for example, one or more alkoxy groups (e.g. p-methoxybenzyl), heterocyclic groups such as tetrahydropyranyl, acyl (e.g. acetyl or benzoyl) and silyl groups such as trialkylsilyl (e.g. t-butyldimethylsilyl or thexyldimethylsilyl).

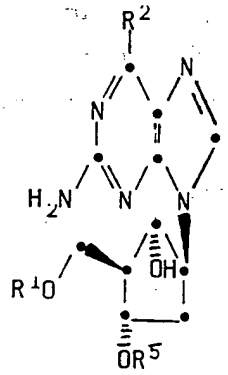
When R^1 represents a hydroxyl protecting group this is conveniently an aralkyl group such as benzyl.

When R^2 represents a protected hydroxyl group the protecting group is conveniently an alkoxyalkyl group such as methoxyethyl.

When compounds of formula (II) contain a protected hydroxyl group at the 3'-position, the protecting group is conveniently a substituted aralkyl group such as an alkoxy substituted benzyl group (e.g. p-methoxybenzyl). Removal of the protecting group may conveniently be

carried out under acidic conditions, for example using trifluoroacetic acid or by reaction with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) followed by treatment with an acid (e.g. hydrochloric acid).

Compounds of formula (II) containing a protected hydroxyl group at the 3'-position may be prepared from a compound of formula (IV)

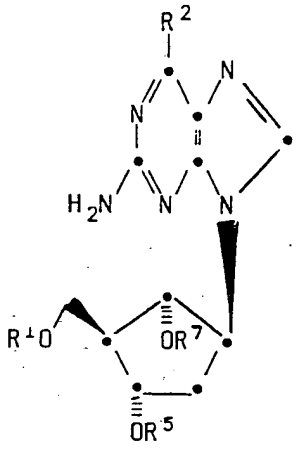


(IV)

(wherein R^2 is as defined previously and R^1 and R^5 are hydroxyl protecting groups) by reacting the said compound of formula (IV) to replace the 1-OH group by a hydrogen atom.

Conveniently, this reaction is effected by (i) reacting the compound of formula (IV) to convert the 1-OH group to a leaving group removable by reduction (e.g. by homolytic reduction) and (ii) reducing said compound to replace the leaving group by a hydrogen atom.

A particularly convenient means of effecting the reaction is to react the compound of formula (IV) with a compound of formula $HalC(=S)OR^6$ (where Hal is a halogen atom, e.g. chlorine, and R^6 is C_{1-6}alkyl, aryl such as phenyl, heteroaryl such as imidazole or C_{1-6}alkylaryl such as p-tolyl) to provide a compound of formula (V)



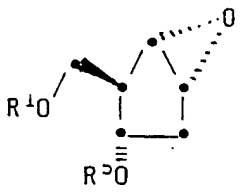
(V)

(wherein $-OR^7$ represents a group $OC(=S)OR^6$ and R^1, R^2 and R^5 are as defined previously), and thereafter reducing the compound of formula (V) using, for example, an alkyltin hydride (e.g. tri-n-butyltin hydride) in the presence of a radical initiator such as a peroxide, azobisisobutyronitrile or light to provide a compound of formula (II) in which the 3-position is substituted by a protected hydroxyl group.

The reaction of a compound (IV) to introduce the R^7 group in the compound (V) may be effected in the presence of a suitable base such as an amine (e.g. pyridine or 4-dimethylaminopyridine) and in a solvent such as a halogenated hydrocarbon (e.g. dichloromethane), conveniently at a reduced temperature (e.g. about -30 to -10°C).

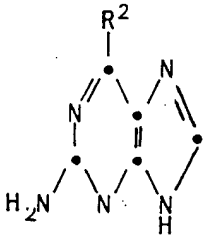
The reduction reaction to provide the desired compound of formula (II) may conveniently be carried out in a suitable solvent, such as pyridine or toluene when an alkyltin hydride is the reducing agent, and the reaction may preferably be carried out at an elevated temperature

Compounds of formula (IV) may be prepared by reacting a compound of formula (VI)



(VI)

(wherein R^1 and R^5 are hydroxyl protecting groups) with a purine base having the formula (VII) -



(VII)

(wherein R^2 is as previously defined) in the presence of a suitable base.

Bases which may be used include alkali metal hydrides, such as sodium hydride, and the reaction may be effected in the presence of a suitable solvent, conveniently dimethylformamide when sodium hydride is the base. It may be desirable to carry the reaction out at an elevated temperature (e.g. 50^0-120^0C) and in the presence of a crown ether (e.g. 15-crown-5).

Intermediates of formula (VII) are known compounds. Intermediates of formula (VI) in which R^5 represents a hydrogen atom are either known compounds described by S. M. Roberts et al., in J. Chem. Soc. Perkin I, 1988, 549 or may be prepared by methods analogous to the methods therein for preparing the known compounds of formula (VI) in which R^5 is a hydrogen atom. Compounds of formula (VI) in which R^5 is a hydroxyl protecting group may be prepared from the corresponding compounds of formula (VI) in which R^5 is a hydrogen atom by standard protection means.

Intermediates of formulae (IV) and (V) are novel compounds and form further aspects of the present invention.

Salts (e.g. physiologically acceptable salts) of the compound of formula (I) may be prepared form the corresponding free base according to the methods described in GB-A-2217320.

It is to be understood that individual steps in the process described hereinabove and sequential combinations of such steps represent further aspects of the present invention.

The following exmaples illustrate the invention but should not be construed as a limitation thereof.

Intermediate 1

(1S,2R,3S,5R)-3-((4-Methoxyphenyl)methoxy)-2-(phenylmethoxy)methyl-6-oxabicyclo[3,1,0]-hexane

A solution of [3S-(1α,2β,3α,5α)]-2-((phenylmethoxy)methyl-6-oxabicyclo[3.1.0]hexan-3-ol[1] (30.40g) in tetrahydrofuran (60ml) was added to a stirred suspension of sodium hydride (3.64g) in tetrahydrofuran (120ml) under nitrogen. The mixture was stirred at room temperature for 1 hour and 4-methoxybenzyl chloride (20.6ml) was added, followed by tetrabutylammonium iodide (510mg) and dimethylformamide (30ml). The mixture was heated under reflux for 1½ hours and allowed to cool. After evaporation of most of the solvent, the remainder was diluted with diethyl ether, washed with water and brine, and dried over anhydrous magnesium sulphate. After filtration and evaporation, the residue was purified by column chromatography (Merck 7734 silica gel, eluant diethyl ether-petrol 2:1) to give the title compound as a yellow oil (42.4g). ^{1}H NMR ($CDCl_3$) δ 7.40-7.15, 7H, m; 6.83, 2H, d; 4.48, 2H, s; 4.40, 2H, s; 3.89, 1H, d; 3.80, 3H, s; 3.55, 1H, bs; 3.44, 1H, bs; 3.40, 2H, m; 2.60, 1H, t; 2.08, 2H, m.

1. SM Roberts et al, J. Chem. Soc. Perkin, 1988, 549.

Example 1

(1'R,4'S)-2-Amino-9-(4-(hydroxymethyl)-2-cyclopenten-1-yl)-1,9-dihydro-6H-purin-6-one

(a) (1S,2R,3S,5S)-5-[2,6-Diamino-9H-purin-9-yl]-3-((4-methoxyphenyl)-methoxy)-2-(phenylmethoxy)methyl-1-cyclopentanol

To a stirred suspension of sodium hydride (1.20g) in dimethylformamide (230ml), under nitrogen, was added 2,6-diaminopurine (11.46g) and the mixture was stirred for 1 hour at room temperature. 15-Crown-5 (11.1g) was added, followed by a solution of Intermediate 1 (17.36g) in dimethylformamide (20ml). The mixture was heated at 140°C for 18 hours. After cooling, methanol (20ml) was added and the mixture was evaporated. The residue was taken up in ethyl acetate, washed with water and brine, and then dried over anhydrous magnesium sulphate. After filtration and evaporation, the residue was purified by column chromatography (Merck 7734 silica gel, eluant

chloroform-methanol 15:1) giving the title compound as a tan solid (16.10g). Crystallisation from ethanol gave a pure sample of the title compound. ^{1}H NMR ($CDCl_3$) δ 7.40, 1H, s; 7.20-7.38, 7H, m; 6.85, 2H, d; 5.50, 2H, bs; 4.80, 2H, bs; 4.60, 1H, m; 4.55, 2H, s; 4.45, 2H, d; 4.26, 1H, t; 4.02, 1H, m; 3.78, 3H, s; 3.65, 2H, m; 2.47, 2H, m; 2.21, 1H, m; MS (+ve CI, CH_4) m/e 491 (MH+).

(b) (1S,2R,3S,5S)-5-[2,6-Diamino-9H-purin-9-yl]-3-((4-methoxyphenyl)-methoxy)-2-(phenylmethoxy)methyl-1-cyclopentanol, phenoxythiocarboxylate

To a stirred solution of the product of part (a) above (10.00g) in dichloromethane (150ml) was added 4-dimethylaminopyridine (4.98g) and the solution was chilled to -45°C. Phenyl chlorothionoformate (3.40ml) was then added dropwise and the mixture was then stirred at -30°C for 2 hours, and then kept for 64 hours at -22°C. The solution was diluted with dichloromethane, washed with water, saturated aqueous sodium bicarbonate solution and brine, and then dried over anhydrous magnesium sulphate. After filtration and evaporation, the residue was purified by column chromatography (Merck 7734 silica gel, eluant chloroform-methanol 20:1) to give the title compound as a light yellow gum (10.07g). ^{1}H NMR ($CDCl_3$) δ 7.58, 1H, s; 7.20-7.40, 10H, m; 6.85-7.00, 4H, m; 6.15, 1H, m; 5.40, 2H, bs; 5.19, 1H, m; 4.65, 2H, bs; 4.59, 2H,s; 4.50, 2H, s; 4.16, 1H, m; 3.82, 5H, m; 2.70, 2H, m; 2.40, 1H, m.

(c) (1'R,3'S,4'R)-9-[3-((4-Methoxyphenyl)methoxy)-4-(phenylmethoxy) methyl-cyclopentan-1-yl]-9H-2,6-purinediamine

To a stirred solution of the product of part (b) above (11.83g) in toluene (180ml) under nitrogen, was added 2,2'-azobis (2-methylpropionitrile) (600mg) followed by tributyltin hydride (8.12ml) and the solution was degassed by bubbling a stream of nitrogen through it for 10 minutes. The mixture was then heated at 90°C for 2 hours. Evaporation gave a residue which was purified by column chromatography (Merck 7734 silica gel, eluant chloroform-methanol 20:1) to give the title compound as a white solid (7.50g). Crystallisation from ethyl acetate gave a pure sample of the

title compound, ,m.p. 132-4°C; $[\alpha]_D^{22}$ + 22.1° (c = 0.98, $CHCl_3$); 'H NMR ($CDCl_3$) δ 7.75, 1H, s; 7.20-7.40, 7H, m; 6.86, 2H, d; 5.31, 2H, bs; 4.92, 1H, m; 4.64, 2H, bs; 4.53, 2H, s; 4.44, 2H, d; 4.04, 1H, m; 3.80, 3H, s; 3.55, 2H, d; 2.49, 2H, m; 2.30, 2H, m; 1.90, 1H, m.

(d) (1S,2R,4R)-4-[2,6-Diamino-9H-purin-9-yl]-2-(phenylmethoxy)methyl-1-cyclopentanol

Trifluoroacetic acid (70ml) was added to the product of part (c) above (7.20g) and the resulting red solution was stirred at ambient temperature for 75 minutes. The solution was slowly added to saturated aqueous sodium bicarbonate solution (1200ml) and then extracted thrice with chloroform. The combined chloroform extracts were washed with brine and dried over anhydrous magnesium sulphate. After filtration and evaporation, the residue was purified by column chromatography (Merck 7734 silica gel, eluant chloroform-methanol 9:1) to give the title compound as a light yellow solid (3.79g). Crystallisation from chloroform gave a pure sample of the title compound. 'H NMR ($CDCl_3$) δ 7.55, 1H, s; 7.34, 5H, m; 5.40, 2H, bs; 4.97, 1H, m; 4.69, 2H, bs; 4.56, 2H, s; 4.44, 1H, m; 3.68, 1H, dd; 3.56, 1H, t; 2.34, 4H, m; 1.80, 1H, m; MS (+ve CI, CH_4) m/e 355 (MH+).

(e) (1S,2R,4R)-4-[2,6-Diamino-9H-purin-9-yl]-2-(phenylmethoxy)methyl-1-cyclopentanol, methanesulphonyl ester

To a stirred, ice-chilled solution of the product of part (d) above (3.58g) in dichloromethane (340ml) under nitrogen, was added 4-dimethylaminopyridine (2.48g). Methanesulphonyl chloride (1.01ml) was added, dropwise, and the solution was stirred for 60 minutes at 0°C. The mixture was diluted with chloroform and washed with water, saturated aqueous sodium bicarbonate solution and brine, and then dried over anhydrous magnesium sulphate. After filtration and evaporation, the residue was purified by column chromatography (Merck 7734 silica gel, eluted with chloroform-methanol 12:1) to give the title compound (4.64g) as a colourless foam. Preparative thin layer chromatography gave a pure sample of the title compound. ' H N M R

($CDCl_3$) δ 7.55, 1H, s; 7.37, 5H, m; 5.33, 2H, bs; 5.25, 1H, m; 4.92, 1H, m; 4.62, 2H, bs; 4.57, 2H, m; 3.63, 2H, m; 3.00, 3H, s; 2.58, 4H, m; 2.02, 1H, m.

(f) (1'R,4'S)-9-[4-(Phenylmethoxy)methyl-2-cyclopenten-1-yl]-9H-2,6-purinediamine

To a stirred suspension of sodium hydride (1.11g) in dimethylformamide (90ml) under nitrogen, was added 2-methoxyethanol (3.74ml), and stirring was continued for 2 hours. The resulting suspension was cooled to 0^0 and a solution of the product of part (e) above (4.44g) in dimethylformamide (50ml) was added with stirring. After 1 hour, the ice-bath was removed and stirring continued for 45 minutes. The mixture was then partitioned between chloroform and water, and the organic layer was subsequently washed with water and brine, dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by column chromatography (Merck 7734 silica gel, eluted with chloroform-methanol 20:1) to give the title compound as a gum (1.80g). H NMR ($CDCl_3$) δ 7.60, 1H, s; 7.30, 5H, m; 6.15, 1H, m; 5.85, 1H, m; 5.60, 2H, bs; 5.55, 1H, m; 4.84, 2H, bs; 4.52, 2H, s; 3.48, 2H, m; 3.10, 1H, m; 2.80, 1H, dt; 1.68, 1H, dt.

(g) (1"R,4"S)-N-[6-Amino-9-(4-acetoxy)methyl-2-cyclopenten-1-yl)-9H-purin-2-yl]-acetamide

To a stirred ice-chilled suspension of the product of part (f) above (1.79g) in acetic anhydride (60ml) under nitrogen, was added dropwise boron trifluoride etherate (2.01ml). After 10 minutes, the ice bath was removed and stirring was continued for 1 hour, whereupon more boron trifluoride etherate (0.67ml) was added. After a further 1 hour, the reaction mixture was slowly poured into saturated aqueous sodium bicarbonate solution (360ml), which was then extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by column chromatography (Merck 7734 silica gel, eluant chloroform-methanol 20:1) to give the title compound as a yellow solid (1.29g). Crystallisation foam ethanol gave a pure sample

of the title compound, m.p. 225-6°; $[\alpha]_D^{22}$ - 154.0° (c = 1.00, $CHCl_3$) ^1H NMR ($CDCl_3$) δ 9.51, 1H, bs; 7.73, 1H, s; 6.15, 1H, m; 5.97, 1H, m; 5.60, 1H, m; 4.14, 2H, m; 3.18, 1H, m; 2.85, 1H, dt; 2.61, 3H, s; 2.06, 3H, s; 1.70, 1H, dt.

(h) (1S,4R)-4-[2,6-Diamino-9H-purin-9-yl]-2-cyclopentenemethanol

The product of part (g) above (1.14g) was suspended in ethanol (120ml) and 2M aqueous sodium hydroxide solution (5.1ml) was added. The mixture was then heated at 40°C for 3 hours, cooled and evaporated. The white residue was purified by column chromatography (Merck 7734 silica gel, eluted with chloroform-methanol 5:1) to give the title compound as a white solid (750mg). Crystallisation from isopropanol gave a pure sample of the title compound. ^1H NMR (d^6 DMSO) δ 7.63, 1H, s; 6.75, 2H, bs; 6.10, 1H, m; 5.84, 3H, m; 5.36, 1H, m; 3.43, 2H, m; 2.85, 1H, m; 2.60, 1H, dt; 1.58, 1H, dt.

(i) (1'R,4'S)-2-Amino-9-(4-(hydroxymethyl)-2-cyclopenten-1-yl)-1,9-dihydro-6H-purin-6-one

To a solution of the product of part (h) above (112mg) in pH7.5 buffer (7.5ml) (from 0.5M disodium orthophosphate, adjusted with orthophosphoric acid) was added adenosine deaminase (28μl, 44 units) in 50% glycerol - 0.01M potassium phosphate, pH6.0, and the solution was warmed at 37°C for 5 days. The resulting white precipitate was filtered off and recrystallised from hot water to give the title compound white crystals (26mg) m.p. 265-70°C (decomp.); $[\alpha]_D^{22}$ -43.1° (c = 0.32, DMSO); ^1H NMR (d^6 DMSO) δ 10.55, 1H, bs; 7.58, 1H, s; 6.44, 2H, bs; 6.10, 1H, m; 5.85, 1H, m; 5.32, 1H, m; 4.74, 1H, t; 3.43, 2H, m; 2.86, 1H, m; 2.60, 1H, dt; 1.58, 1H, dt.

Example 2

(1'R,4'S)-2-Amino-9-(4-(hydroxymethyl)-2-cyclopenten-1-yl)-1,9-dihydro-6H-purin-6-one

(a) (1S,2R,3S,5S)-5-[2-Amino-6-(2-methoxyethoxy)-9H-purin-9-yl]-3-((4-methoxyphenyl)methoxy)-2-(phenylmethoxy)methyl-1-cyclopentanol

To a stirred suspension of lithium hydride (195mg) in dimethylformamide (90ml) under nitrogen was added 2-amino-6-methoxyethoxy purine (7.15g) and the suspension was heated at 120°C for 1h and then cooled to ambient temperature. To this solution was added a solution of Intermediate 1 (8.06g) in dimethylformamide (60ml) and the mixture was heated at 145°C for 3½ hours. After cooling to ambient temperature, the solvent was removed and the residue was taken up in ethyl acetate. This mixture was washed with water, and brine, dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by column chromatography (Merck 7734 silica gel, eluted with ethyl acetate-ethanol 9:1) to give the title compound as a white solid (6.92g). Crystallisation from ethyl acetate gave a pure sample of the title compound, m.p. 118-20°C; $[\alpha]_D^{22}$ -5.74° (c = 1.61, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.52, 1H, s; 7.40-7.20, 7H, m; 6.86, 2H, d; 4.88, 2H, bs; 4.65, 3H, m; 4.53, 2H, s; 4.46, 2H, bs; 4.25, 1H, t; 4.01, 1H, m; 3.80, 5H, m; 3.64, 2H, m; 3.42, 3H, s; 2.54, 1H, m; 2.43, 1H, m; 2.28, 1H, m.

(b) (1S,2R,3S,5S)-5-[2-Amino-6-(2-methoxyethoxy)-9H-purin-9-yl]-3-((4-methoxyphenyl)methoxy)-2-(phenylmethoxy)methyl-1-cyclopentanol, phenoxythiocarboxylate

To a magnetically stirred solution of the product of part (a) above (8.04g) and dimethylaminopyridine (2.85g) in dichloromethane (85ml) under nitrogen at 0°C was added phenylchlorothionoformate (1.95ml), dropwise. The mixture was stirred at 0°C for 15 minutes then at ambient temperature for 30 minutes. A further aliquot of phenylchlorothionoformate (0.1ml) was added and stirring continued for an additional 20 minutes. The reaction mixture was diluted with dichloromethane and then washed with water, saturated aqueous sodium bicarbonate and brine. The organic solution was dried over anhydrous magnesium sulphate, filtered and the solvent removed. The residue was purified by column chromatography (Merck 7734 silica gel, eluant chloroform-ethyl acetate 1:1) to give the title compound (9.01g) as a colourless foam. ^1H NMR ($CDCl_3$) δ 7.64, 1H, s; 7.40-7.20, 10H, m; 6.92, 4H, m; 6.17, 1H, t; 5.20, 1H, m; 4.81, 2H, bs; 4.63, 2H, t;

4.57, 2H, s; 4.50, 2H, s; 4.14, 1H, m; 3.80, 7H, m; 3.42, 3H, s; 2.68, 2H, m; 2.40, 1H, m.

(c) (1'R,3'S,4'R)-6-(2-Methoxyethoxy)-9-[3-((4-methoxyphenyl) methoxy)-4-(phenylmethoxy)methyl-cyclopentan-1-yl]-9H-purin-2-amine

To a magnetically stirred solution of the product of part (b) above (9.01g) in toluene (140ml) under nitrogen was added 2,2'-azobis(2-methylpropionitrile) (500mg) and tributyltin hydride (5.64ml). The mixture was degassed and then heated at 90°C for 1¾ hours. A further aliquot of 2,2'-azobis(2-methylpropionitrile) (154mg) and tributyltin hydride (1.8ml) were added and the mixture heated at 100°C for 1 hour. The mixture was allowed to cool overnight and then evaporated. The residue was purified by column chromatography (Merck 7734 silica gel, eluant ethyl acetate-ethanol 9:1) to give the title compound (5.56g) as a gum. ^{1}H NMR ($CDCl_3$) δ 7.64, 1H, s; 7.40-7.20, 7H, m; 6.87, 2H, d; 4.95, 1H, m; 4.80, 2H, bs; 4.63, 2H, t; 4.52, 2H, s; 4.45, 2H, s; 4.04, 1H, m; 3.69, 5H, m; 3.53, 2H, m; 3.42, 3H, s; 2.60-2.20, 4H, m; 1.85, 1H, m.

(d) (1S,2R,4R)-4-[2-Amino-6-(2-methoxyethoxy)-9H-purin-9-yl]-2-(phenylmethoxy)methyl-1-cyclopentanol

To a magnetically stirred solution of the product of part (c) above (5.43g) in dichloromethane-water (200ml, 19:1) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2.78g). The mixture was stirred vigorously overnight. The reaction mixture was diluted with dichloromethane and repeatedly washed with saturated aqueous sodium bicarbonate. The combined aqueous washings were back extracted with dichloromethane. The combined organic extracts were washed with brine and the solvent removed. The residue was dissolved in hydrochloric acid (2N) and washed with ethyl acetate. The organic washings were extracted with hydrochloric acid (2N). The combined aqueous extract was basified (pH 9) by addition of solid sodium carbonate and then extracted with dichloromethane. The organic solution was washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by column chromatography (Merck 7734 silica gel, eluant chloroform-methanol 9:1) to afford a brown

3.48, 2H, d; 3.43, 3H, s; 3.10, 1H, m; 2.80, 1H, dt; 1.65, 1H, dt; MS (+ve CI, CH_4) m/e 396 (MH^+, B^+), 364, 210.

(g) (1"R,4"S)-N-[1,9-Dihydro-9-(4-((acetoxy)methyl)-2-cyclopenten-1-yl)-6-oxo-6H-purin-2-yl]-acetamide

To a magnetically stirred solution of the product of part (f)(ii) or (f)(iii) above (2.39g) in acetonitrile (40ml) under nitrogen was added a solution of aluminium triiodide (0.52M; 18.0ml) in acetonitrile. The mixture was heated at reflux for 2 hours and allowed to cool overnight. The mixture was diluted with methanol and the resultant solution evaporated. The residue was purified by column chromatography (Merck 7734 silica gel, eluant chloroform-methanol 9:1) to afford a gum. This was dissolved in acetic anhydride (25ml) and cooled to 0^0C. The stirred solution was treated with boron trifluoride etherate (0.76ml), dropwise, under nitrogen. The mixture was stirred at 0^0C for 10 minutes and then at ambient temperature for 1½ hours. The mixture was poured into aqueous saturated sodium bicarbonate solution and the product extracted into ethyl acetate. The organic extracts were washed with brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed. The residue was purified by column chromatography (Merck 7734 silica gel, eluant chloroform-methanol 19:1) to afford the crude product. This was triturated with diethyl ether and dried in vacuo to give the title compound (265mg) as a fawn powder. M.p. 144-6^0C; $[\alpha]_D^{23}$ + 4.96^0 (c = 1.25, $CHCl_3$) ^{1}H NMR ($CDCl_3$) δ 12.05, 1H, bs; 9.80, 1H, bs; 7.70, 1H, s; 6.07, 1H, m; 5.83, 1H, m; 5.44, 1H, m; 4.59, 1H, dd; 4.22, 1H, dd; 3.21, 1H, m; 2.76, 1H, dt; 2.34, 3H, s; 2.11, 3H, s; 1.81, 1H, dt.

(h) (1'R,4'S)-2-Amino-9-(4-(hydroxymethyl)-2-cyclopenten-1-yl)-1,9-dihydro-6H-purin-6-one

To a stirred solution of the product of part (g) above (157mg) in methanol (5ml) was added a saturated solution of ammonia in methanol (30ml). The mixture was stirred at ambient temperature overnight. The solution was evaporated and the residue purified by column chromatogrpahy (Merck 7734 silica gel, eluant chloroform-methanol 4:1)

to afford the crude product. Recrystallisation from water gave the title compound (75mg) as white crystals. M.p. 272-4^{0}C (decomp.), $[\alpha]_D^{23}$ -68^0 (c = 0.40, MeOH); ^{1}H NMR (d^6 DMSO) δ 10.58, 1H, bs; 7.59, 1H, s; 6.45, 2H, bs; 6.61, 1H, m; 5.85, 1H, m; 5.33; 1H, m; 4.74, 1H, t; 3.44, 2H, t; 2.87, 1H, m; 2.58, 1H, dt; 1.57, 1H, dt.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 90/01199

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: C 07 D 473/00

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	C 07 D 473/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	EP, A, 0267878 (CIBA-GEIGY) 18 May 1988 see pages 19-24, claims; particularly compounds V and VII --	7
A	US, A, 4605659 (J.P.H. VERHEYDEN) 12 August 1986 see columns 23-26, claims --	7
A	Journal of the Chemical Society, Chemical Communications, no. 14, 1987, The Royal Society of Chemistry, (London, GB), K. Biggadike et al.: "Short convergent route to homochiral carbocyclic 2'-deoxynucleosides and carbocyclic ribonucleosides", pages 1083-1084 see pages 1083-1084, formula 6 --	7

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* Special categories of cited documents: [10]

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
9th October 1990	25. 10. 90
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	R.J. Eernisse

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, ** with indication, where approoriate, of the relevant passages	Relevant to Claim No.
P,A	FR, A, 2626002 (REGENTS OF THE UNIVERSITY OF MINNESOTA) 21 July 1989 see front-page; pages 54-56, claims & GB, A, 2217320 (cited in the application)	1-6

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9001199 SA 39043

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 23/10/90
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